

**Utility Patent
Ser. No. 10/564,861**

REMARKS

Claims 1-4 and 6-13 and 15 are pending at a mailing of the March 2, 2009 Final Office Action. Claims 1 and 10 are amended. Claims 11-13 and 15 are cancelled. No new matter is introduced. A withdrawal of all rejections is respectfully requested.

Claim Objections

Examiner objects to Claims 1, 4 and 6-13 for incorrect wording. Applicant submits the appropriate corrections to comply with examiner's objection. Withdrawal of the objection is respectfully requested.

Claim Rejections - 35 U.S.C. §112, second paragraph:

Examiner rejects Claims 1-4 and 6-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention.

Examiner rejects Claims 1 and 15 because the phrase "certain oncological diseases" fails to establish the metes and bounds of the claim. Applicant amends Claims 1 and 15 to exclude the disputed term.

Examiner rejects Claim 1 because the term "gastric, and colon cancer" fails to clarify whether both gastric cancer and colon cancer are separate or single alternatives of the disease to be treated. Applicant amends Claim 1 by deleting the treatment of such condition.

Withdrawal of the rejection is respectfully requested.

**Utility Patent
Ser. No. 10/564,861**

Claim Rejections - 35 U.S.C. § 112, first paragraph:

Examiner rejects Claims 1-4, 6-13 and 15 under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for Erlich carcinoma, lung carcinoma, and malignant and low differentiated lymphoma, does not reasonably provide enablement for treating all other oncological diseases with DNase and anti-DNA antibodies.

More specifically, Examiner maintains that claims are overly broad and the specification fails to provide working examples of sufficient scope to provide enablement of the claimed invention. Applicant amends the independent claims to exclude the treatment of diseases Examiner alleges is not sufficiently enabled in the specification. Specifically, Applicant deletes the treatment of "breast cancer, gastric cancer and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma", leaving the treatment for lung carcinoma, and malignant and low differentiated lymphoma in the independent claims. The treatment of those two conditions is, by Examiner's admission, sufficiently enabled.

Examiner rejects Claims 1-4, 6-13 and 15 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, Examiner objects that the claim terms "breast cancer, gastric and colon cancer, kidney cancer, pancreatic cancer, malignant melanoma" are species of an "oncological diseases" genus. Applicant amends the independent claims to exclude such terms. As amended, independent claims 1 and 15 only include the terms "lung carcinoma, and malignant and low differentiated lymphoma," which, by Examiner's admission, are sufficiently described in the specification.

Withdrawal of the rejection is respectfully requested.

Utility Patent
Ser. No. 10/564,861

Claim Rejections - 35 USC § 102:

Claim 15 is rejected under 35 U.S.C. §102(b) as being anticipated by Sugihara et al. (Br. J. Cancer, 1993, 67, 66-70).

Applicant cancels claim 15. Withdrawal of the rejection is respectfully requested.

Claim Rejections - 35 USC § 103:

Claims 1, 4, 6 and 9 are rejected under 35 U.S.C. §103(a) as being obvious over Sugihara et al. (Br. J. Cancer, 1993, 67, 66-70).

Examiner argues that Sugihara et al. teach that DNase can be used to prevent liver metastases. Further, Examiner argues that even though Sugihara et al. do not teach specific dosage regimens recited in claims 1, 4, 6 and 9, a skilled artisan would have been motivated to optimize the dosage and treatment schedule through routine optimization. (emphasis added).

Applicant disagrees with this contention. Dose levels of claim 1 cannot be achieved by "routine optimization" The best of current art in pharmacology dictates that only knowledge of pharmacodynamics and exposure-response relationships may provide basis for "Dose Optimization". [REF 5 and REF 6]

1. Pharmacodynamics (PM): Knowledge of what the drug does to the body. PD covers desirable and undesirable effects, from biomarkers to surrogates to clinical endpoints.
2. Exposure-response analysis covers the knowledge of concentration-effect relationship.

**Utility Patent
Ser. No. 10/564,861**

That mean that skilled artisan may optimize dosage and treatment through optimization only if he has knowledge of pharmacodynamics and exposure-response relationship of DNASE. In our case that means that until skilled artisan will be aware of necessity to destroy blood extracellular DNA he will never have the grounds to increase the dose of DNASE for 16 000 times versus conventional dose.

That is illustrated by the following clinical research work:

1. DNASE enzyme available in medical practice in USA for physicians for already 40 years and since its discovery in middle of 20th century is used almost exclusively to treat Cystic fibrosis by inhalation (REF3). Several oncologists did try to use DNASE in cancer chemotherapy in humans, but attempts have failed. [Minerva Med.1977 Apr 30;68(21),p.1447; REF8]

The authors did try several increasing DNASE doses but consider treatment ineffective with small palliation only due to known anti-inflammatory action of deoxuribonuclease. They did not go for further dose escalation and that fully supports inventor position that increasing the dose few orders of magnitude is totally outside the category " of routine optimization". The physician need to know pharmacodynamics an exposure -response knowledge of the drug to be able to imagine 16 000 dose increase.

It is important to underline that current strategy of dose optimization teach to minimize the dose rather than to increase it.

2. Dose levels of claim 1 are critical to the curative action of DNASE. Sugihara has observed some lifespan prolongation, which is obviously not a cure. A lot of different compounds

Utility Patent
Ser. No. 10/564,861

(hundreds of thousands) may show some life-span prolongation in cancer bearing mice; however only few of them show efficacy in cure of human cancer (REF 2). That is why the immaterial effect observed by Sugihara does not trigger the further development of DNASE as anti-cancer drug. Disease stabilization or regression is ONLY measure of objective cure (REF 1). That might be achieved with DNASE only based on claimed dose levels. Thus claimed dose levels are critical to achieve cure.

Thus, we cannot not agree claimed dose levels are not critical and that 16000 fold increase of dose may be anticipated by skilled person, until skilled person knows the necessity to destroy extracellular DNA.

Even much less significant dose modifications in pharmacology may lead to significant inventive steps, leading to new quality of cure; such matters are recognized as patentable, due to general unpredictability in the field. Administration of effective dose, based on knowledge of mechanism of action is critical in pharmacology and pharmacological treatment of medical disorders.

FDA Guidance for Industry (ICH-E4; REF4) specifically stated:

[k]nowledge of the relationships among dose, drug concentration, drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important to the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best ways to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide the added benefit or would produce unacceptable side effects." (FDA Guideline for Industry: Dose-Response Information to Support Drug Registration, ICH-F4, November 1994, pg. 1). The review (REF 7) shows how the improper target selection leads to drug failures.

Utility Patent
Ser. No. 10/564,861

Discovery of novel action modalities (new targets) with subsequent adjustment of doses and regimes of treatment may lead to new quality of treatment of conditions with previously known medicaments, much less effective previously.

Discovery of novel targets and/or action modalities with pharmacologically appropriate dosing and regimes may lead to previously ineffective in treatment of condition medicaments became effective.

Such matters are patentable. That is in particular illustrated by granted US patents:

- US Patent 7,511,028 by Brookler provides a method of treating otosclerosis in a human in need thereof by administering a bisphosphonate in a defined dosing schedule. The invention demonstrates an effective response and sustained benefit in the treatment of otosclerosis. Particularly, the method involves administration of a bisphosphonate in a stepped-up dosage amount, e.g., in a dose that is at least one and a half times the recommended dose for osteoporosis. What is claimed:
 1. A method of treating otosclerosis in a human in need thereof which comprises administering to the human a bisphosphonate in an amount that is at least about 150% of a recommended dose for osteoporosis in said human, wherein the bisphosphonate is administered in divided doses at least two times a week.
- US Patent 7,511,019 by Whitehouse is directed to a unit dose comprising 0.2 .mu.g/kg to 36 .mu.g/kg of a recombinant FGF. That which is claimed is a method for treating a human patient for coronary artery disease, comprising administering into one or more coronary vessels in a human patient in need of treatment for coronary artery disease a therapeutically effective amount of a recombinant fibroblast growth factor (FGF). The Applicants have discovered that a fibroblast growth factor, , when administered as a unit dose of about 0.2 .mu.g/kg to about 36 .mu.g/kg into one or more coronary vessels (IC) of a human patient in need of coronary angiogenesis, unexpectedly provides the human patient with a rapid and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an unexpectedly superior increase in the treated patient's exercise tolerance time (ETT).
- US Patent 7,473,687 by Hoffman provides Methods for the treatment of a traumatic central nervous system injury with known protective drug progesterone. The methods comprise a therapy comprising a constant or a two-level dosing regime of progesterone. In one method, a subject in need thereof is administered at least one cycle of therapy, wherein the cycle of therapy comprises administering a therapeutically effective two-level intravenous dosing regime of progesterone. The two-level dosing regime comprises a first

Utility Patent
Ser. No. 10/564,861

time period, wherein a higher hourly dose of progesterone is administered to the subject, followed by a second time period, wherein a lower hourly dose of progesterone is administered to the subject.

- US Patent 7,419,949 by Hedner provides methods for preventing and/or treating bleeding episodes by administering a single dose of Factor VIIa or a Factor VIIa equivalent. Preferably, the single dose comprises between about 150 and about 500 .mu.g/kg Factor VIIa or Factor VIIa equivalent. The invention claimed is:
 1. A method for treating a bleeding episode in a human subject in need of such treatment, said method comprising administering intravenously to said human subject purified Factor VIIa, wherein said administering is in a single dose and said dose comprises a single-dose-effective amount of said Factor VIIa, wherein said single-dose-effective amount comprises between 250 and 500 .mu.g/kg Factor VIIa and wherein, subsequent to said administration, no further Factor VIIa is administered to said subject for a period of at least 4 hours. This new dosing of previously known pro-coagulant provides new quality of bleeding cure.
- US Patent 7,427,609 by Leonard discloses a method for treating conditions related to hormone deficiencies comprising continuously administering at least one estrogen and at least one progestin wherein the amount of estrogen is substantially constant and the amount of progestin is decreased in at least one step from an amount sufficient to establish a nonproliferative endometrium to an amount that maintains the nonproliferative endometrium. The invention particularly relates to methods for treating physical conditions related to vasomotor symptoms, brought about by the onset of menopause. The method of the invention provides a method of treating a subject by administering a therapeutically effective amount of two or more dosage levels of progestin wherein the dosage levels of progestin decrease stepwise during the treatment period. The conditions treated include vasomotor symptoms, atrophic vaginitis, and osteoporosis, among others. The discovery of new treatment regimen utilizing known medicaments under this patent lead to new quality of treatment of gynecological disorders.
- US Patent 7,204,996 by Androctt discloses method of treating a subject having relapsed or refractory cancer such as leukemia with liposomal annexin including the steps of (a) evaluating the subject to determine if the subject has relapsed or refractory cancer, (b) administering a high-dose amount of liposomal-annexin for at least 3 days in a 7 day period. Invention claiming a method of treating a human subject having leukemia comprising the step of administering a dose of at least about 250 mg/m² of liposomal annexin for at least 3 days in a 7 day period. Application of high dose annexin incorporated in liposomes (alternative delivery mechanism requiring high dose load) leads to outstanding therapeutic result- overcoming of P-glycoprotein mediated resistance.
- US Patent 6,903,100 by Rowe discloses treatment of multiple sclerosis by periodically administering a high dose of methotrexate at a level sufficiently high to cross the blood brain barrier. The invention provides a method for treating MS, and other non-infectious, non-neoplastic inflammatory conditions of the CNS, by periodically administering a high

Utility Patent
Ser. No. 10/564,861

dose of methotrexate in an amount sufficient to cross the BBB. It was discovered that periodic treatment (versus known sporadic treatment) with high doses unexpectedly provides long term suppression of the disease. Thus, long-term keeping high doses of the drug is critical to provide effective care. Thus, sporadic high dose methotrexate treatments can allow the accumulation of destructive immune cells in the CNS between treatments, which prevents long term inhibition of the disease. By periodically purging the CNS of the destructive immune cells, the periodic high dose treatments of the present invention prevent the disease from progressing and thereby provide long term inhibition of the disease.

- US Patent 5,962,459 by Piazza discloses unexpected therapeutic effects of known compound uridine, when used in high doses. It was showed that uridine shows important trophic properties on various types of cultured cells, stimulating cell reproduction when used at rather high dose levels. A method for the treatment of disturbances of the nervous system due to degeneration of neuronal or glial cells in mammals, comprising administering to said mammals an effective amount of uridine at a dosage of 300 to 2000 mg/day to counteract said degeneration by stimulating cell growth was claimed.
- US Patent 6,846,496 by Timonen discloses method for the prevention or treatment of postmenopausal osteoporosis by initiating the treatment with a low dose of an estrogenic compound and increasing the dose of the estrogenic compound after the initiation period. The inventors surprisingly discovered that when treating postmenopausal osteoporosis by initiating the treatment with a low dose of an estrogenic compound and increasing the dose of the estrogenic compound after this initiation period, the increase in bone mineral density was higher than when treating postmenopausal osteoporosis by administering the same dose of the estrogenic compound (either the low dose or the increased dose) for the whole term of the treatment.

What is important, even discovery of methods teaching how to determine optimal dosing and schedules of drug administration to treat condition are of great value for medical cure.

That is illustrated by issued USA patents:

- US patent 7,465,551 by Blumenthal provides kits and methods for evaluating the myelosuppressive state of a patient. These methods and kits provide a useful adjunct for cytotoxic and myelosuppressive therapies. By establishing threshold levels of certain cytokines as a surrogate for myelosuppression, treatment protocols can be optimized to reduce myelotoxicity, while maximizing effective dose. Measured levels of one or more

Utility Patent
Ser. No. 10/564,861

cytokines in a patient subjected to cytotoxic therapy, relative to a normal population, may be used to determine the dose of a hematopoietic cytokine to be administered to the patient.

The state of the art in pharmacology dictates that only knowledge of pharmacodynamics and exposure-response relationships may provide basis for dose optimization. Such dosage and treatment optimization is hardly a product of routine practice. One of ordinary skill in the art may optimize dosage and treatment only by having sufficient knowledge of pharmacodynamics. In the present case, one of ordinary skill in the art will be aware of the necessity to destroy blood extracellular DNA; however, the dosage requirement will hardly be a product of routine optimization. The dose of DNase in the present case is increased 16,000 times over the conventional dose. Such difference in the order of magnitude can be not be characterized as resulting from routine optimization. One of ordinary skill in the art must know pharmacodynamics and exposure-response characteristics of the drug before contemplating a 16,000 dose increase. Sugihara et al. neither teach nor suggest any motivation why the dose should be increased by such an order of magnitude.

Therefore, Applicant contends that Examiner has not shown that one of ordinary skill in the art could achieve the present invention through routine optimization. As such, Independent claim 1 should be found allowable. As the independent claim is allowable, so should all dependent claims be found allowable. Withdrawal of the rejection is respectfully requested.

**Utility Patent
Ser. No. 10/564,861**

Claims 12-13 are rejected under 35 U.S.C. §103(a) as being obvious over Sugihara et al. as applied above in view of Leland et al. (Chem. & Bio., 2001, 8, 405-13).

Applicant cancels Claims 12 and 13. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the amendments submitted herein and the above comments, it is believed that all the grounds of rejection are overcome and that the application has now been placed in full condition for allowance. Should there be any further questions, Examiner is urged to telephone Applicant's undersigned attorney at (330) 253-2225.

Respectfully Submitted,



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Utility Patent
Ser. No. 10/564,861

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